Effects of β-adrenergic blockade and stimulation on airways in normal subjects

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Summary
The effects of propranolol and salbutamol on conventional pulmonary function tests and closing volume have been studied in ten normal subjects. Propranolol and salbutamol had minor effects on measurements of airways resistance but had no effect on closing volume which is particularly sensitive to changes in peripheral airways. It was concluded that propranolol had negligible overall effect on central and peripheral airways properties in normal subjects, and it would appear that β-adrenergic activity has little measurable influence on peripheral airways in normal man at rest.

Introduction
It is well known that β-blockers can produce bronchoconstriction in asthmatics (McNeill, 1964) and propranolol has a greater effect than practolol in this respect (Macdonald and McNeill, 1968). However, there is a difference of opinion about the influence of β-blockers in people with normal lungs. Some workers have found evidence of bronchoconstriction induced by propranolol (McNeill and Ingram, 1966; Macdonald, Ingram and McNeill, 1967) but other workers have failed to find this (Zaid and Beall, 1966; Marcelle et al., 1968; Richardson and Sterling, 1969; Tattersfield, Leaver and Pride, 1973). The question is of some importance because of the widespread and prolonged use of β-blockers in the treatment of hypertension, angina, and cardiac arrhythmias.

The conventional techniques for measuring airway resistance are relatively insensitive to changes in calibre of the smaller airways. This is because the greater part of the airway resistance resides in the central airways (Macklem and Mead, 1967) and there has to be considerable damage to the peripheral airways before the FEV₁ or airway conductance becomes abnormal (Hogg, Macklem and Thurlbeck, 1968). It is therefore possible that β-blockers may cause constriction in the peripheral airways which is not readily detected. Furthermore, prolonged administration of these drugs over many years might produce irreversible changes within the lungs.

Recently, newer techniques have become available for assessing damage to the peripheral airways. Tattersfield et al. (1973) used dynamic compliance to assess the influence of propranolol on peripheral airways but could find no effect. The present work was undertaken to study the effect of propranolol and salbutamol on peripheral airways as measured by the technique of closing volume (Collins, 1973). The effect of FEV₁ and airways conductance, as measured with the body plethysmograph, was also studied.

Material and method
Ten normal subjects, eight male and two female, aged 20 to 30 years, were studied before and after 10 mg propranolol was given by i.v. injection over 3 min. Five of these subjects were also studied before and after 500 μg salbutamol given by a metered aerosol. Two of the subjects smoked between five and ten cigarettes per day and another smoked a pipe, but the remainder were non-smokers. The subjects were volunteers from the hospital staff and all gave informed consent to the procedure.

Forced expiratory volume in 1 sec (FEV₁) and forced vital capacity (FVC) were measured by a spirometer, the best of three attempts being taken. Airways resistance and thoracic gas volume were determined by body plethysmography (Dubois, Botelho and Comroe, 1956) from which specific conductance (SGaw) was derived. The mean of four readings was taken. Residual volume (RV) was measured by a helium dilution technique.

Closing volume was then measured by monitoring the expired nitrogen concentration after a single inspiration of oxygen from RV (Anthonisen et al., 1969). At RV the airways in the dependent region of the lungs are closed even in healthy people and the regional RV in this area is therefore much lower than
that in the non-dependent region. Consequently, inspiration of 100% oxygen to TLC results in a lower nitrogen concentration in the dependent regions compared with the non-dependent regions. In the subsequent expiration from TLC the nitrogen concentration shows a sudden increase as the airways close in these dependent regions with a high oxygen concentration. The point at which this closure occurs is known as the closing point and the volume of air expired after that point is known as the phase IV volume.

The nitrogen concentration was measured at the mouthpiece using a respiratory mass spectrometer (20th Century Electronics) and expired volume was recorded from a potentiometer attached to a spirometer. Inspiratory and expiratory flow rates were monitored via a pneumotachograph and displayed on a meter which the subject could see. By this means the subject kept the flow rate below 0.5 l/sec. The records of nitrogen concentration and expired volume were displayed separately on a 2-channel recorder from which the measurements were made. ‘Closing volume’ is expressed as the ratio of phase IV vol/VC. Only those subjects with a clear closing point were selected for this study (approximately 50% of those screened).

The mean of three closing volumes, together with measurement of FEV1 FRC, RV and SGaw were obtained before propranolol was given. Thereafter, single values of closing volume were obtained at 5-min intervals after the start of the injection for up to 30 min. Repeat measurements of FEV1, FVC, RV and SGaw were then made between 30 and 45 min after the injection. The pulse rate was measured before each closing volume manoeuvre. Each measurement was made in the same sequence for each subject.

The mean of three closing volumes, together with FEV1 and FVC were also obtained before salbutamol was given. Single closing volume measurements were made 5, 15 and 30 min after the start of the inhalation of the salbutamol and FEV1 and FVC measurements were repeated at 30 min.

Results

The effect of propranolol and salbutamol on the conventional lung function parameters are shown in Table 1. It can be seen that propranolol produces a small but significant drop in FEV1 and FVC, but the FEV1/FVC ratio was un influenced. However, there was a small but significant reduction in SGaw suggesting bronchoconstriction. One subject showed an unusually large fall in SGaw to 56% of the control level. If this result is excluded, no significant difference between the pre- and post-propranolol values was found. This subject was a cigarette smoker but had no chest symptoms and had negative intradermal skin tests. Salbutamol produced a small but significant increase in FEV1/FVC although the individual changes in FEV1 and FVC were not significant. Neither propranolol nor salbutamol had any significant effect on RV.

Propranolol 10 mg produced a reduction in pulse rate which was still highly significant at 30 min (paired t test P = <0.001) (Table 2). However, no significant effect on closing volume could be demonstrated at any time up to 30 min after injection of propranolol (Table 2). Similarly, salbutamol had no influence on closing volume up to 30 min after inhalation (Table 3).

Discussion

The present work has shown a small but significant fall in FEV1 with propranolol. Although Turner et al.

<p>| TABLE 1. The effect of propranolol and salbutamol on conventional pulmonary function tests |
|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Significance (P)</th>
<th>Before</th>
<th>After</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (litres)</td>
<td>4·00±0·20</td>
<td>3·89±0·20</td>
<td>&lt;0·01</td>
<td>4·19±0·41</td>
<td>4·35±0·41</td>
<td>NS</td>
</tr>
<tr>
<td>FVC (litres)</td>
<td>4·90±0·26</td>
<td>4·79±0·30</td>
<td>&lt;0·05</td>
<td>4·93±0·50</td>
<td>4·88±0·51</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>82±2</td>
<td>82±2</td>
<td>NS</td>
<td>85±2</td>
<td>90±2</td>
<td>&lt;0·05</td>
</tr>
<tr>
<td>RV (litres)</td>
<td>1·57±0·15</td>
<td>1·55±0·10</td>
<td>NS</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>SGaw KPA/l/sec.</td>
<td>0·25±0·03</td>
<td>0·22±0·03</td>
<td>&lt;0·05</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Mean ± 1 s.d. of mean significance by paired t test. NS = Not significant.

<p>| TABLE 2. The effect of propranolol on closing volume and heart rate |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Control</th>
<th>5 min</th>
<th>10 min</th>
<th>15 min</th>
<th>20 min</th>
<th>25 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closing vol. (%)</td>
<td>9·8±0·7</td>
<td>7·6±1·3</td>
<td>10·3±1·1</td>
<td>8·9±0·9</td>
<td>9·3±1·5</td>
<td>11·2±2·4</td>
</tr>
<tr>
<td>Pulse rate/min</td>
<td>80±4</td>
<td>62±2</td>
<td>63±3</td>
<td>63±3</td>
<td>64±2</td>
<td>65±2</td>
</tr>
</tbody>
</table>

Mean ± 1 s.d. of mean.
(1971) have also demonstrated a small fall in \( FEV_1 \) with propranolol, other workers have failed to find this (McNeill and Ingram, 1966; Tattersfield et al., 1973; Zaid and Beall, 1966). The divergent results could be due to differences in dosage or population studied since the effect is obviously small. If \( FEV_1 \) is expressed as a ratio with FVC there is no longer any significant effect.

Although airway conductance appeared to decrease with propranolol the fall was not significant if the one subject with a pronounced response to propranolol is excluded. Richardson and Sterling (1969) found that three out of their ten normal subjects showed a fall in conductance with propranolol but, over their series as a whole, the decrease was not significant. Any effect of propranolol on airways calibre as measured by \( FEV_1 \) and \( SG_{aw} \) would, therefore, seem to be small and probably negligible.

There was clearly no evidence of an influence of propranolol on closing volume. A rise in RV with propranolol could obscure an increase in absolute volume at which the airways closed but the present work has shown no influence of propranolol on RV. The evidence suggests that in normal subjects at rest there is insufficient sympathetic tone on the peripheral airways to be influenced by \( \beta \)-blockade.

In addition, \( \beta \)-stimulation with salbutamol failed to influence closing volume thus confirming the findings of Collins et al. (1973). The sympathetic system appears not to have a strong influence on peripheral airways in normal man, although in the dog, \( \beta \)-blockade has a greater influence on peripheral rather than central airways (Woolcock et al., 1969). This may reflect species differences but, alternatively, the tone of the muscles in peripheral airways may not significantly influence the closing volume. Bouhys and van de Woestijne (1971) have suggested that the smooth muscle tone in peripheral airways may protect them from compression during expiration. Therefore, \( \beta \)-stimulation, whilst producing bronchodilatation in the airways, may increase their tendency to be compressed. These two effects are likely to influence closing volume in opposing directions and the overall effect of \( \beta \)-stimulation and blockade on closing volume may be negligible for this reason.

Tattersfield et al. (1973) could find no effect of propranolol on peripheral airways as measured by dynamic compliance and partial expiratory flow volume curves. The present work, using closing volume as an index of the state of the peripheral airways, is consistent with these results. There is, therefore, no evidence that propranolol has a deleterious effect on peripheral airways in subjects with normal lungs.

**Table 3. The effect of salbutamol on closing volume**

<table>
<thead>
<tr>
<th>Control</th>
<th>1 min</th>
<th>15 min</th>
<th>30 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closing vol. (%)</td>
<td>12.1 ± 1.7</td>
<td>11.0 ± 1.9</td>
<td>10.4 ± 1.2</td>
</tr>
</tbody>
</table>

Mean ± 1 s.d. of mean.

References


McNEIL, R.S. (1964) Effect of a \( \beta \) adrenergic-blocking agent, propranolol, on asthmatics. Lancet, II, 1101.


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